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10/727,195

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Carmen V. Pepicelli

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EXAMINER

HOWARD, ZACHARY C

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/727,195	Applicant(s) PEPICELLI ET AL.	
	Examiner ZACHARY C. HOWARD	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 April 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3,4 and 25-35 is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 32-34 is/are allowed.
- 6) ☒ Claim(s) 1,3,4,25-31 and 35 is/are rejected.
- 7) ☒ Claim(s) 1 is/are objected to.
- 8) ☒ Claim(s) 1,3,4 and 25-31 are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 16 May 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>1/21/09</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 4/20/09 has been entered in full. Claims 27 and 29-31 are amended. Claims 2 and 5-24 were previously canceled. New claims 32-35 are added. Claims 1, 3, 4 and 25-35 are under consideration in the instant application.

Information Disclosure Statement

The Information Disclosure Statement of 1/21/09 has been considered.

Withdrawn Objections and/or Rejections

The following page numbers refer to the previous Office Action (9/29/08).

The rejections of claims 27 and 28 under 35 U.S.C. § 103(a) at pg 7-9 as being unpatentable over Marigo et al (U.S. Patent No. 6,261,786) in view of Bellusci (1997) and further in view of Cardoso et al (1996) is *withdrawn* in view of Applicants' amendments to the claims. However, please see below the new rejection of these claims under 35 U.S.C. § 103(a) necessitated by Applicants' amendments to the claims.

The rejection of claims 29-31 under 35 U.S.C. § 112, first paragraph at pg 9-11 for failing to provide enablement for the claims is *withdrawn* in view of Applicants' amendments to the claims. However, please see below the new rejection of these claims under 35 U.S.C. § 112, first paragraph for new matter necessitated by Applicants' amendments to the claims.

Maintained Objections and/or Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 3, 4, 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marigo et al (U.S. Patent No. 6,261,786, published 7/17/01, filed 7/2/96 and claiming priority to 12/30/93; cited previously) in view of Fujita et al (9/18/1997, Biochemical and Biophysical Research Communications, 238: 658-665; cited previously). This rejection was set forth previously and maintained at pg 2-5 of the 9/29/08 Office Action.

Applicants' arguments (1/21/09; pg 5-6) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response, Applicants argue that "nowhere in Marigo et al, or in Fujita et al, is there any hint or suggestion to create a method that comprises determining, and evaluating relative to an appropriate control, both whether the agent inhibits or attenuates hedgehog signaling and whether the agent inhibits or reduces cell proliferation or growth" (pg 5). Applicants argue that the statement from Marigo et al quote in the rejection "seems to imply that their screens are to be used for either identifying agonists or antagonists of the normal cellular function of the subject hedgehog polypeptides or that these screens are to be used to determine the role of hedgehog agonists/antagonists in the pathogenesis of disease" (pg 5).

Applicants' arguments have been fully considered but are not found persuasive. It is maintained that the claimed method directed to screening assays in which two parameters are evaluated is obvious over the teachings of Marigo et al in view of the teachings of Fujita et al. As acknowledged previously, it is true that Marigo and Fujita each teach different parameters for use in screening. However, the rejection under 103(a) is not based on the teachings of either reference alone, but rather on the teachings of Marigo in view of the teachings of Fujita. Practicing the method of Marigo et al alone would identify an antagonist of hedgehog signaling but would not indicate whether said antagonist inhibits the growth of the lung cancer cells taught by Fujita et al. Practicing the method of Fujita et al alone would identify an antagonist of the growth of lung cancer cells but would not indicate whether said antagonist inhibits hedgehog signaling. However, in view of the teachings of Marigo in view of Fujita it would have been immediately obvious to combine the teachings of the two references to screen to

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identify molecules that inhibit the hedgehog pathway (as taught by Marigo) and then to screen for those that inhibit cellular growth (as taught by Fujita). Marigo et al provides motivation to develop an assay to identify hedgehog signaling antagonists of cellular proliferation by teaching, "this present invention facilitates the development of assays which can be used to screen for drugs, including hedgehog homologs, which are either agonists or antagonists of the normal cellular function of the subject hedgehog polypeptides, or of their role in the pathogenesis of cellular differentiation and/or proliferation and disorders related thereto" (col 48, lines 40-46)). It is true that this statement from Marigo quoted in the rejection presents an alternative. However, said alternative is either (1) the development of assays for the identification of agonists or antagonists of the normal function of hedgehog, or (2) the development of assays for the identification of agonists or antagonists of the role of hedgehog in disease. Thus, this teaching provides motivation for developing assays that identify modulators of hedgehog signaling in normal or in diseased tissue. In the instant rejection, this teaching provides motivation as to why the person of ordinary skill in the art would have combined the teachings of Marigo et al with Fujita et al to develop an assay for the identification of antagonists of the role of hedgehog in the growth of lung cancer cells. It is therefore maintained that the combined teachings of Marigo and Fujita satisfy the criteria set forth in MPEP 2142 to establish a *prima facie* case of obviousness.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 29-31 and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection was set forth previously at pg 11 of the 9/29/08 Office Action for claims 29-31; new claim 35 is herewith added.

Applicants' arguments (1/21/09; pg 8) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

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In the response, Applicants argue that the claims have been amended and "[b]y focusing on proteins involved in patched-mediate signaling other than patched, claims 29-31 serve to appropriately limit the claims from which they depend" (pg 8).

Applicants' arguments have been fully considered but are not found persuasive. Claim 29 depends from claim 1 and previously recited "wherein the agent disrupts the association of patched with smoothened". As amended claim 29 now recites "wherein the agent interacts with a protein other than patched". This amendment does not render the claim definite; the claim remains indefinite for the same reason set forth in the previous Office Action: it is unclear how the limitation relates to the agent used in the method of the parent claim. The method of the parent claim encompasses the use of a broad genus of agents, some of which are identified by the method as agents that inhibit hedgehog signaling and reduce cell proliferation. It is unclear how the characteristic recited in claim 29 limits the agents of claim 1. Specifically, it is unclear whether: (1) the characteristic recited in claim 29 limits the agents to be used (screened) in the method to compounds already known to interact with a protein other than patched; or (2) the characteristic recited in claim 29 limits the identified agents to those that are then determined to interact with a protein other than patched.

Claims 30, 31 and 35 are rejected for the same reason as claim 29.

New objections

Specification

The disclosure is objected to because of the following informalities:

At page 16, line 4, the word "squamous" is misspelled as "squamus".

Appropriate correction is required.

Claim Objections

Claim 26 is objected to because of the following informalities:

In claim 26, the word "squamous" is misspelled as "squamus".

Appropriate correction is required.

New rejections necessitated by Applicants' amendment

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 27 and 28 rejected under 35 U.S.C. 103(a) as being unpatentable over Marigo et al (U.S. Patent No. 6,261,786, published 7/17/01, filed 7/2/96 and claiming priority to 12/30/93; cited previously) in view of Bellusci (January 1997. Development. 124: 53-63; cited as reference CB on the 12/3/03 IDS) and further in view of Cardoso et al (1996. Developmental Dynamics. 207: 47-59) and further in view of Schuger et al (1993. Developmental Biology. 159: 462-473).

Claims 27 and 28 were previously rejected under 103(a) as being unpatentable over Marigo et al in view of Bellusci and further in view of Cardoso et al (pg 7-9 of the 9/29/08 Office Action). Applicants' amendments to claim 27 (adding "and which lung cells are not present in the culture as part of a tissue or organ") necessitate withdrawal of said rejection. However, said amendments also necessitate the new ground of rejection under 103(a) set forth herein.

The recitation of "screening for an agent for inhibiting or reducing the proliferation or growth of cells" in the preamble of claim 27 is interpreted as an intended use and bears no accorded patentable weight to distinguish the claimed method over one from the prior art. Therefore, claim 27 encompasses a method comprising contacting cultured non-cancerous lung cells, wherein said cells are not present in the culture as part of a tissue or organ, with an agent and determining as compared to a control, whether the agent inhibits (1) hedgehog/patched signal transduction and (2) cell proliferation. Claim 28 depends from claim 27 and limits the agent to a small organic molecule.

Marigo teaches "cell-based assays for identifying small molecule agonists/antagonists" (col 51, lines 24-25) and that the test compound can be a "small organic molecule" (column 10, line 60). Marigo teaches that "cells which are sensitive to hedgehog induction, e.g. patched-expressing cells, can be contacted with a hedgehog

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protein and a test agent of interest, with the assay scoring for anything from simple binding to the cell to modulation in hedgehog inductive responses by the target cell in the presence and absence of the test agent. As with the cell-free assays, agents which produce a statistically significant change in hedgehog activities (either inhibition or potentiation) can be identified" (col 51, lines 27-35). Marigo teaches that patched gene expression is responsive to Shh signaling. Marigo teaches that "[a]fter identifying certain test compounds as potential modulators of the target hedgehog receptor activity, the practitioner of the subject assay will continue to test the efficacy and specificity of the selected compound both in vitro and in vivo ... for subsequent in vivo testing ... agents identified in the subject assay can be formulated in pharmaceutical preparations for in vivo administration to an animal, preferably a human". Marigo further teaches that, "the present invention facilitates the development of assays which can be used to screen for drugs, including hedgehog homologs, which are either agonists or antagonists of the normal cellular function of the subject hedgehog polypeptides, or of their role in the pathogenesis of cellular differentiation and/or proliferation and disorders related thereto" (col 48, lines 40-46).

Marigo does not teach a method of screening using cultured lung cells that are not lung cancer cells or that the cultured cells are not present in the culture as part of a tissue or organ. Marigo does not teach a method of screening that includes both determining whether the agent inhibits or attenuates hedgehog signaling and determining whether the agent inhibits cell proliferation or growth.

Bellusci teaches "a role for SHH in lung morphogenesis, and suggest that SHH normally regulates lung mesenchymal cell proliferation in vivo" (see Summary on pg 53). Bellusci teaches that "Shh overexpression results in an increase in epithelial and mesenchymal cell proliferation and to a lung which contains an abundance of mesenchyme and no functional alveoli" (pg 54). Bellusci teaches measurement of cell proliferation using BrdU incorporation, comparing the transgenic cells to normal cells as a control (pg 55; results shown in Table 1 on page 57). Bellusci further teaches that the "level of *Ptc* transcripts was clearly increased in the mesenchyme of the transgenic

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lung" (pg 58). Bellusci does not teach cultured lung cells, or that the cultured cells are not present in the culture as part of a tissue or organ.

Cardoso et al teaches cultured lung cells that are not lung cancer cells. On page 48, Cardoso teaches techniques for embryonic lung cell culture using lung explants from rats sacrificed at gestational day 13.5. The cultured lungs exhibit "airway branching and differentiation of both epithelium and mesenchyme, reproducing the overall proximal-to-distal pattern seen in lung in vivo" (pg 49). Cardoso further teaches contacting the embryonic lung culture with a small organic molecule (retinoic acid) that increases hedgehog signaling (as opposed to the inhibition required by the instant methods). Cardoso does not teach that the cultured cells are not present in the culture as part of a tissue or organ.

Schuger et al teach cultured lung cells that are not present in the culture as part of a tissue or organ. Specifically, Schuger et al teach mesenchymal and epithelial cell monocultures and cocultures derived from the lungs of embryonic/fetal mice at gestational ages 12 to 17 (pg 463, left column). Schuger et al further teach the effects of retinoic acid (RA) on proliferation of epithelial and mesenchymal cells in monoculture and coculture (pg 466, left column). Schuger et al teach that "mixed lung cell populations in coculture spontaneously sorted into epithelial and mesenchymal compartments while rearranging themselves into a pattern resembling the tissue of origin ... [w]hen these cocultures were exposed to RA, the epithelia clusters grew larger than in controls" (pg 466). Schuger et al teach that "[m]esenchymal monocultures exposed to RA exhibited an increase in cell proliferation, which was maximal with concentrations of 0.5 and 1 μ M and decreased with higher levels of RA" (pg 466).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to create transgenic mice that overexpress Shh as taught by Bellusci, prepare an embryonic lung cell culture from said mice using the technique taught by Schuger, and to contact said lung cell culture with a test agent that is a small organic molecule as taught by Marigo, and to measure hedgehog signaling pathway (by measuring patched gene expression) as compared to a control as taught by Marigo (i.e., in the presence and absence of the test compound) and to further measure growth

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by BrdU incorporation as compared as taught by Bellusci as compared to a control (i.e., cells from normal mice). Marigo provides motivation to identify hedgehog signaling antagonists that are also antagonists of cellular proliferation in normal tissue by teaching, "the present invention facilitates the development of assays which can be used to screen for drugs, including hedgehog homologs, which are either agonists or antagonists of the normal cellular function of the subject hedgehog polypeptides, or of their role in the pathogenesis of cellular differentiation and/or proliferation and disorders related thereto" (col 48, lines 40-46). Bellusci, Cardoso and Schuger in combination provide a reasonable expectation that hedgehog signaling would be active and subject to modulation in isolated embryonic lung cells in monoculture or coculture because (1) Bellusci show that Shh overexpression increases embryonic lung cell proliferation *in vivo*; (2) Cardoso teach that retinoic acid increases hedgehog signaling in embryonic lung explant cultures; and (3) Schuger teaches that retinoic acid increases proliferation of isolated embryonic lung cells in monoculture or coculture. The person of ordinary skill in the art would have been motivated to do so to identify a small organic molecule that is an antagonist (inhibitor) of hedgehog signaling and lung cell growth, as such can be used to inhibit hedgehog-dependent proliferation (as taught by Marigo).

Claim Rejections - 35 USC § 112, 1st paragraph, new matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 29-31 and 35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement because the claims contain new matter.

Claims 29-31 depend from claims 1, 27 and 28 (respectively) and were each amended 4/20/09 to limit the parent claim to "wherein the agent interacts with a protein other than patched". New claim 35 depends from new claim 32 and limits the parent

claim in the same fashion. Applicants' response filed 1/21/09 indicates that support for the amendment can be found in ¶175 and 182 of the published application.

The Examiner has reviewed the referenced paragraphs as well as the specification in general. The specification at ¶175 describes cell-based assays for identifying agonists and antagonists in which cells are contacted with a hedgehog protein and a test agent of interest, and that agents which produce a change in hedgehog activities (inhibition or potentiation) can be identified. However, there is no conception of a genus of agents that interact with a protein other than patched. The specification at ¶182 describes gene products that are implicated in "patched-mediated signal transduction" including patched, cubitus interruptus, fused, costal-2, smoothened and suppressor of fused. Elsewhere, the specification (¶178) teaches that the gene products smoothened, costal-2 and/or fused can be coexpressed with patched in a reagent cell. However, this portion of the specification does not indicate that the agent that modulates hedgehog signaling actually interacts with one of these agents as opposed to patched. Elsewhere, the specification (¶176) teaches that agents that disrupt the association of patched and smoothened can be identified. However, this portion of the specification does not specifically indicate that the agent that disrupts association of patched and smoothened actually interacts with smoothened as opposed to interacting with patched. Furthermore, even if the specification taught that the agent interacted with one or more of patched, cubitus interruptus, fused, costal-2, smoothened and suppressor of fused, this would still not provide support for a genus of agents that "interact with a protein other than patched". The genus of proteins "other than patched" is not defined in the instant specification, and has been broadly interpreted as encompassing any of the thousands of proteins expressed by a lung cancer cell other than patched. Thus, even teaching interaction with one or more proteins other than patched would not provide support for this vast genus. Throughout the specification there is no conception of a subset of agents that interact with a protein other than patched, nor does the concept of the specific genus flow naturally from the disclosure of the specification. Therefore, the specification as originally filed lacks support for the genus of molecules encompassed by the amended claims.

Conclusion

Claims 32-34 are allowable.

The Examiner has not identified any prior art that anticipates or renders obvious the method of new claims 32-34. These claims include the limitation that the lung cancer cells used in the method are "not squamous cell carcinoma cells". The use of non-squamous cell carcinoma cells is taught in ¶168 of the published application, which teaches that the methods of inhibition of lung cancer cells of the invention can be practiced with small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) including adenocarcinoma, lung cell carcinoma and squamous cell carcinoma. Lung cancer cells that are SCLC, as well as NSCLC cells that are adenocarcinoma or lung cell carcinoma, meet the definition of cells that are not squamous cell carcinoma as recited in the claims. Fujita et al (1997) (used in the rejection of claims 1, 3, 4, 25 and 26 under 35 USC 103(a) as being unpatentable over Marigo et al (US 6,261,786) in view of Fujita et al) teaches that Sonic hedgehog (Shh) mRNA was expressed in human lung squamous carcinoma cells lines, weakly expressed in some lung adenocarcinoma cell lines, and not expressed in lung small cell carcinoma cell lines (pg 660, left column). Furthermore, Fujita et al teach that the adenocarcinoma cells, despite expressing Shh mRNA weakly, do not proliferate in response to Shh-N protein (as measured by BrdU incorporation) (pg 661, right column). In this regard, the adenocarcinoma cells are similar to the small cell carcinoma cells rather than the lung squamous cell lines, which do proliferate in response to Shh-N. Thus, while it would be obvious to use the lung squamous cell lines taught by Fujita in the method of screening of claims 1, 3, 4, 25 or 26, the skilled artisan would not have been motivated to substitute adenocarcinoma or lung small cell carcinoma cells for the squamous cells in view of Fujita et al teaching that these cell lines are not responsive to the hedgehog protein. Furthermore, the relevant art published after Fujita et al has found that hedgehog signaling is actually active and responsive to the hedgehog protein in some small cell and non-small cell lung cancers (including both adenocarcinoma and squamous cell carcinoma). Watkins

et al (2003) teach that a "subset of small-cell lung cancer (SCLC) ... maintain their malignant phenotype in vitro and in vivo through ligand-dependent Hh pathway activation" (Abstract of Watkins et al, 2003. Nature. 422: 313-317). Yuan et al (2007) teach that "[d]uring a screen of a panel of 60 human tumor cell lines with a HH antagonist, we observed that the proliferation of a subset of NSCLC cell lines was inhibited ... [t]hese NSCLC cell lines express HH, as well as key HH target genes, consistent with them being activated through an autocrine mechanism" (see Abstract of Yuan et al, 2007. Oncogene. 26: 1046-1055).

Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For

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more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Z. C. H./

Examiner, Art Unit 1646

/Bridget E Bunner/

Primary Examiner, Art Unit 1647